Drug-Induced Aseptic Meningitis Associated With Intrathecal Trastuzumab

Journal of Pharmacy Technology
2014, Vol. 30(2) 43–47
© The Author(s) 2013
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/8755122513500918
pharmatech.sagepub.com

Craig W. Freyer, PharmD¹, George Yaghmour, MD²,
Katherine Jennings, PharmD³, and Vishnuprabha Dhanapal, PharmD, BCPS, BCOP²

Abstract

Objective: To report a case of drug-induced aseptic meningitis (DIAM) in a patient receiving intrathecal trastuzumab (ITT) for leptomeningeal carcinomatosis (LC) secondary to HER-2/neu positive breast cancer. **Case Summary:** A 43-year-old female with stage IV breast cancer presented with headache, paresthesias, and aphasia. Brain imaging suggested leptomeningeal enhancement. Adenocarcinoma cells were found on cerebrospinal fluid analysis, and infectious etiologies were excluded. The patient received 30 mg of ITT via Ommaya reservoir and suffered sudden neurologic deterioration within 2 hours. Given the sudden onset of clinical deterioration after ITT administration, it was determined that the patient had suffered from DIAM. The patient suffered progressive neurologic decline and was unable to care for herself any further. **Discussion:** Treatment for LC remains challenging due to limited clinical experience and the challenging location of the disease. ITT has been used in multiple reports without adverse events. A temporal relationship existed between ITT administration and significant neurologic deterioration, possibly related to DIAM. Our patient was not exposed to any more common causative agents of DIAM. Reasons for her lack of recovery are likely multifactorial. Symptoms of DIAM may have in part been exacerbated by progressive LC; however, prior to ITT, symptoms had shown slow but persistent progression rather than significant, acute changes in severity. Retrial of the offending agent was not attempted due to patient risk; thus, a cause-and-effect relationship cannot be established. This event is a “possible” drug-induced adverse event scoring 2 on the Naranjo algorithm. **Conclusions:** Use of ITT for LC has been frequently reported in recent literature with substantial efficacy and lack of adverse events. This is the first published report of any significant adverse event associated with ITT. Clinicians need to be aware of the possibility of DIAM with ITT and explore options to prevent or manage this severe complication.

Keywords

trastuzumab, breast cancer, leptomeningeal carcinomatosis, neoplastic meningitis, intrathecal, chemotherapy, aseptic meningitis, chemical meningitis, drug-induced

Introduction

Leptomeningeal carcinomatosis (LC) refers to seeding of the leptomeningeal membrane of the central nervous system (CNS) by solid tumor cells. LC is diagnosed in roughly 5% of metastatic breast cancer cases and carries a median survival of less than 3 months with death resulting from progressive neurologic deterioration.^{1–3} Tumor cells access the leptomeningeal membrane via hematogenous dissemination, lymphatic spread, or by direct extension, resulting in symptoms such as headache, mental status changes, cranial nerve palsies, hemiparesis, diplopia, and motor weakness.^{1,3} Diagnosis of LC depends on cerebrospinal fluid (CSF) examination via lumbar puncture (LP) of a patient with prior mentioned symptomatology, previous cancer diagnosis, and radiologic findings suggestive of meningeal enhancement.^{1,3} CSF abnormalities are similar to those

found in bacterial meningitis, including elevated opening pressure (>20 cm H₂O), leukocytosis, elevated protein, and decreased glucose; however, the presence of malignant cells is diagnostic of LC.³ The optimal treatment of LC is undefined due to limited evidence and clinical experience. Treatment strategies include focal radiation, systemic chemotherapy, and intrathecal chemotherapy. Commonly used chemotherapy agents for LC include intrathecal methotrexate, intrathecal cytarabine, thiopeta, or intravenous

¹Roswell Park Cancer Institute, Buffalo, NY, USA

²Henry Ford Hospital, Detroit, MI, USA

³University of Illinois at Chicago, IL, USA

Corresponding Author:

Craig W. Freyer, PharmD, Department of Pharmacy, Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, USA.
Email: Craig.Freyer@RoswellPark.org

high-dose methotrexate.¹ Trastuzumab (Herceptin) is a less studied preservative-free alternative treatment for LC from HER-2/neu positive breast cancer. Trastuzumab acts to inhibit proliferation of HER-2/neu expressing breast cancer cells; however, its systemic use may increase the risk of brain metastases.⁴⁻⁶ Molecules with a molecular mass more than 200 Da have poor CNS penetration; as such, systemic trastuzumab (185 kDa) may create a tumor sanctuary site within the CNS.⁶⁻⁸ The use of intrathecal trastuzumab (ITT) has been described in multiple published case reports using doses up to 150 mg without any significant adverse effects.⁸⁻¹⁹ We describe a patient who developed drug-induced aseptic meningitis (DIAM) within 2 hours of a single dose of ITT.

Patient Case

The patient was a 43-year-old African American female who presented with 7 days of frontal headache, anorexia, vomiting, weakness, bilateral digital paresthesias, ataxia, and expressive aphasia. She denied changes in vision. Her past oncologic history was significant for stage IV metastatic inflammatory breast ductal carcinoma. Her past medical history was significant for type 2 diabetes mellitus, diabetic gastroparesis, and hypertension. At presentation, magnetic resonance imaging (MRI) of her brain and an LP were performed. Imaging suggested leptomeningeal metastases. CSF analysis showed elevated protein, low glucose, 5 red blood cells, 26 white blood cells (26% were lymphocytes, 4% neutrophils), and 58 adenocarcinoma cells, suggesting LC. Infectious etiologies were excluded by negative bacterial and viral cultures of the CSF and negative polymerase chain reaction (PCR) assay for herpes simplex virus (HSV) on 2 separate occasions.

The patient was diagnosed with estrogen receptor positive, stage IIIc inflammatory, invasive ductal carcinoma. The sample was strongly positive for HER-2/neu on immunohistochemistry. Following her diagnosis, she received 6 cycles of neoadjuvant carboplatin, docetaxel, and trastuzumab followed by a modified radical mastectomy, post-mastectomy chest wall radiation, and adjuvant weekly intravenous trastuzumab and tamoxifen. After 8 months of trastuzumab and tamoxifen therapy, the patient developed metastases to the lung and liver and developed a malignant pericardial effusion, which was drained. At that time, the patient was changed to a combination of lapatinib, capecitabine, and goserelin. Trastuzumab and tamoxifen were discontinued. After 8 months of therapy, the patient demonstrated progressive disease on imaging studies and was changed to protein-bound paclitaxel and bevacizumab for 1 cycle with disease progression. Next, therapy was changed to gemcitabine and bevacizumab, of which the patient received 3 cycles. On further disease progression, therapy was changed to ixabepilone and bevacizumab, of which the patient received 2 cycles prior to the current

hospitalization. Her most recent dose of chemotherapy was 9 days prior to admission. Throughout her treatment course, all chemotherapy agents were administered at FDA-approved or National Comprehensive Cancer Network–recommended dosages and cycle durations. Unfortunately, the patient failed to achieve durable responses to multiple chemotherapy agents and was admitted with active, uncontrolled disease. About 3 months prior to admission, the patient had an MRI without contrast of her brain, which was negative for metastasis. On admission, the patient was taking the following medications: metformin 500 mg by mouth twice daily, metoprolol tartrate 150 mg by mouth twice daily, metoclopramide 10 mg by mouth 3 times a day prior to meals, and simvastatin 20 mg by mouth at bedtime, all of which the patient had been taking for at least the last 30 days.

On admission, the patient was determined to be a suitable candidate for ITT given her ability to perform activities of daily living and care for herself. Six days after admission, an indium 111 radionuclide cisternogram ruled out CSF flow abnormalities, and an Ommaya reservoir was placed without complications. Prior to ITT, dexamethasone 4 mg intravenous every 6 hours was started, which did yield some improvement in aphasic symptoms and was continued throughout the patient's hospitalization. Twelve days after her admission, she received 30 mg of ITT via Ommaya reservoir, with an initial plan to receive this dose weekly until disease progression. Trastuzumab was selected over more commonly used intrathecal chemotherapy agents (eg, intrathecal methotrexate) due to concerns about methotrexate toxicity and the lack of significant adverse drug events with ITT reported at that time. Although the patient had received systemic trastuzumab in the past, it was thought that the presence of CNS disease was likely related to the inability of trastuzumab to penetrate the CNS when given via the intravenous route. ITT was prepared by a pharmacist specifically trained in preparation of chemotherapy using aseptic technique that complies with USP 797 standards of practice. ITT was prepared by diluting sterile drug to a final volume of 5 mL using preservative-free sterile water for injection rather than the diluent provided by the manufacturer. The Ommaya reservoir was flushed with 5 mL of preservative-free normal saline for injection prior to ITT administration. Within 2 hours of receiving ITT, the patient suffered sudden mental status changes including obtundation, dizziness, urinary incontinence, and severe vomiting. About 4.5 hours after ITT administration, the patient fell and hit her head for which subsequent imaging ruled out intracranial hemorrhage. The Ommaya reservoir was noted to be in place and intact. Small amounts of air in the frontal horns of the lateral ventricles as well as over the right frontal lobe were noted, which were not present on previous imaging and were most likely secondary to Ommaya reservoir use. An electroencephalogram did not suggest seizure

activity. The day after receiving ITT, the patient developed new onset dysphasia. Five days after administration, repeat CSF analysis was positive for 9% malignant adenocarcinoma cells, slightly low glucose levels, elevated protein, 3310 red blood cells, and 50 white blood cells, 21% of which were neutrophils. CSF cultures were negative, and PCR was negative for HSV DNA. Six days after ITT, the patient developed new onset left-sided numbness and paresthesias with delayed reaction time and difficulty following commands. A repeat MRI of her brain was performed, which revealed worsening LC. Given the sudden onset of clinical deterioration that ensued after ITT administration, the primary medical team, neurooncologist, and neurosurgeon determined that the patient had suffered a medication adverse event in the form of DIAM. ITT was discontinued and the patient received 7 sessions of whole brain radiation therapy, all with progressive neurologic impairment. The patient ultimately developed worsening dysphagia, hearing loss, dysarthria, paresthesias, and unsteady gait. The patient was discharged to a nursing home after 5 weeks of hospitalization as she was unable to care for herself any further.

Discussion

Treatment for LC remains challenging due to limited clinical experience, poor performance status of patients diagnosed with the condition, as well as the challenging physiologic location of the disease. Treatment goals are palliative with aims of improving or stabilizing neurological status and prolonging survival. Patients are considered good candidates for aggressive treatment if life expectancy is more than 3 months and are able to carry out activities of daily living mostly on their own.²⁰ Our patient met these criteria given her initial absence of major neurological deficits.

Historically, commonly used intrathecal chemotherapy for management of LC included methotrexate, cytarabine, liposomal cytarabine, and thiotepa. Widespread use of trastuzumab brought reports of successful treatment of LC related to HER2/neu positive breast cancer with ITT, using various schedules and doses ranging from 5 to 150 mg every 3 days to every 3 weeks.⁸⁻¹⁹ ITT combinations with methotrexate, cytarabine, and hydrocortisone¹⁸ as well as prednisolone¹⁹ have been reported with the absence of adverse effects. ITT also caused no significant adverse effects when up to 15 mg weekly was administered via intrathecal infusion to cynomolgus monkeys.²¹ Our patient did not receive intrathecal corticosteroid because this was not described in the literature at the time of drug administration. The majority of case reports of ITT do not describe the concentration of the drug administered into the CSF; however, Stemmler and colleagues reported using a drug concentration of approximately 21 mg/mL without any reported adverse effects.¹² The concentration of ITT used in our

patient case was 6 mg/mL. Despite the lack of adverse effects previously reported, a clear temporal relationship existed in our patient between ITT administration and significant decline in neurologic status, possibly related to DIAM.

DIAM is an uncommon adverse event reported with numerous agents mostly in the form of anecdotal case reports. Drugs most frequently implicated in DIAM include systemically administered sulfamethoxazole/trimethoprim, β -lactam antibiotics, nonsteroidal anti-inflammatory drugs, and intravenous immune globulin.²²⁻²⁵ Our patient was not exposed to any of these more common causative agents during her hospitalization. In general, agents administered intrathecally pose the greatest risk of DIAM; however, agents administered parenterally have also been implicated.²² Intrathecal cytarabine, methotrexate, and thiotepa have been implicated as causes of DIAM²⁰; however, our patient never received any of these agents. Symptoms of DIAM, such as headache, fever, nausea, vomiting, and general malaise, are nonspecific and may mimic those of bacterial meningitis.^{22,23} More serious cases may present with confusion, vertigo, hypotension, photophobia, psychomotor agitation, and seizure-like activity.^{22,23} Such symptoms typically appear within 24 to 48 hours of exposure to the offending agent.²² DIAM can occur on exposure to a drug the patient has previously tolerated,²⁴ as may be the case with our patient who previously tolerated systemic trastuzumab. Most cases follow a relatively benign course and resolve without permanent sequelae within 7 days.^{22,23} The pathophysiology behind DIAM is likely multifactorial, including immune-related hypersensitivity reactions as well as direct irritation of the meninges by the drug.²²⁻²⁵

DIAM is a diagnosis of exclusion in which infectious etiologies are previously excluded. CSF analysis yields a pleocytosis with a neutrophilic predominance, with elevated protein and normal to decreased glucose concentrations.^{20,22,23} The only confirmatory diagnosis of DIAM is rechallenge of the offending agent in a controlled hospital setting; however, such a trial carries significant risks.^{22,25} On discontinuation of the offending agent, symptoms and CSF abnormalities usually resolve. In our case, typical symptoms of DIAM, including headache, nausea, vomiting, and confusion, developed within a reasonable time period after drug administration (roughly 2 hours); however, they did not resolve within the typical time period after drug discontinuation. These mental status changes were a significant decline from previously stated complaints prior to admission.

Reasons for her lack of recovery after discontinuation of ITT may be multifactorial. It is possible that her symptoms of DIAM were in part exacerbated by progressive LC that was nonresponsive to a single dose of ITT; however, prior to ITT administration symptoms had shown slow but persistent progression rather than significant, acute changes in

disease severity. Persistence of symptoms may be related to prolonged drug exposure as it is unknown how long trastuzumab persists in the CSF. Retrial of the offending agent was not attempted due to risk of severe clinical deterioration; thus, a definitive cause-and-effect relationship cannot be established. Repeat LPs were performed on days 2 and 5 post administration of trastuzumab and were consistent with findings typical of DIAM: elevated protein concentrations, leukocytosis with a neutrophil predominance, and low glucose levels. Infectious etiologies were excluded as bacterial cultures and HSV PCR were both negative on 2 separate occasions. Her symptoms could in part be explained by air pocket formation in the frontal horns of the lateral ventricles as well as over the right frontal lobe, which was identified on MRI after ITT administration; however, these pockets were not identified on subsequent MRIs, yet symptoms continued to persist. In addition, aseptic meningitis has been identified as the most common complication of medication administration via Ommaya reservoir.²⁰ Despite this risk, guidelines recommend medication delivery via Ommaya reservoir over serial LPs due to complications associated with the LP procedure, improved drug delivery and pharmacokinetics, lower interpatient variability, and improved patient comfort.¹ Given the temporal relationship of signs and symptoms of DIAM compared to ITT administration, trastuzumab-induced DIAM remains the most likely cause of our patient's clinical deterioration. This adverse event is a "possible" drug-induced adverse reaction with a score of 2 using the Naranjo algorithm,²⁶ taking into account the lack of symptom improvement after drug discontinuation, lack of rechallenge, and other possible explanations for the patient's clinical deterioration.

Conclusion

LC represents a rare but serious complication of metastatic breast cancer for which minimal treatment options exist. In recent years, several reports have described use of ITT alone or in combination with cytotoxic chemotherapy with favorable clinical outcomes and lack of considerable adverse effects. We described the case of a patient diagnosed with LC who developed DIAM after receiving a single dose of 30 mg of ITT—the first significant adverse drug event reported with this agent when administered directly into the central nervous system. Clinicians who care for patients with this rare complication of breast cancer need to be aware of the possibility of DIAM with ITT and explore therapeutic options to prevent or better manage this possible adverse event.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Nabors LB, Ammirati M, Bierman PJ, et al. *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Central Nervous System Cancers (Version 1.2013)*. Fort Washington, PA: National Comprehensive Cancer Network.
2. Yap HY, Yap BS, Tashima CK, DiStefano A, Blumenschein GR. Meningeal carcinomatosis from breast cancer. *Cancer*. 1978;42:283-286.
3. Chamberlain MC. Neoplastic meningitis. *Oncologist*. 2008; 13:967-977.
4. Herceptin (trastuzumab) [package insert]. San Francisco, CA: Genentech, Inc; October 2010.
5. Leyland-Jones B. Human epidermal growth factor receptor 2-positive breast cancer and central nervous system metastases. *J Clin Oncol*. 2009;27:5278-5286.
6. Burstein HJ, Lieberman G, Slamon DJ, Winer EP, Klein P. Isolated central nervous system metastases in patients with HER2-overexpressing advanced breast cancer treated with first-line trastuzumab based therapy. *Ann Oncol*. 2005;16:1772-1777.
7. Pestalozzi BC, Brignoli S. Trastuzumab in CSF. *J Clin Oncol*. 2000;18:2349-2351.
8. Platini C, Long J, Walter S. Meningeal carcinomatosis from breast cancer treated with intrathecal trastuzumab. *Lancet*. 2006;7:778-780.
9. Dumitrescu C, Lossignol D. Intrathecal trastuzumab treatment of the neoplastic meningitis due to breast cancer: a case report and review of the literature. *Case Rep Oncol Med*. 2013;2013:154674. doi:10.1155/2013/154674.
10. Hofer S, Mengele K, Stemmler HJ, Schmitt M, Pestalozzi B. Intrathecal trastuzumab: dose matters. *Acta Oncol*. 2012;51:955-956.
11. Stemmler HJ, Schmitt M, Harbeck N, et al. Application of intrathecal trastuzumab (Herceptin) for treatment of meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer. *Oncol Rep*. 2006;15:1373-1377.
12. Stemmler HJ, Mengele K, Schmitt M, et al. Intrathecal trastuzumab (Herceptin) and methotrexate for meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer: a case report. *Anticancer Drugs*. 2008;19:832-836.
13. Laufman LR, Forsthoefel KF. Use of intrathecal trastuzumab in a patient with carcinomatous meningitis. *Clin Breast Cancer*. 2001;2:235.
14. Colozza M, Minenza E, Gori S, et al. Extended survival of a HER-2-positive metastatic breast cancer patient with brain metastases also treated with intrathecal trastuzumab. *Cancer Chemother Pharmacol*. 2009;63:1157-1159.
15. Ferrario C, Davidson A, Bouganim N, Aloyz R, Panasci LC. Intrathecal trastuzumab and thiopeta for leptomeningeal spread of breast cancer. *Ann Oncol*. 2009;20:792-795.
16. Mir O, Ropert S, Alexandre K, Lemare F, Goldwasser F. High dose intrathecal trastuzumab for leptomeningeal metastases secondary to HER-2 overexpressing breast cancer. *Ann Oncol*. 2008;19:1978-1980.

17. Shojima K, Suzuki E, Saito K, et al. Application of intrathecal trastuzumab for treatment of meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer (Abstract 1138). *J Clin Oncol*. 2008;26:75S.
18. Mego M, Sycova-Mila Z, Obertova J, et al. Intrathecal administration of trastuzumab with cytarabine and methotrexate in breast cancer patients with leptomeningeal carcinomatosis. *Breast*. 2011;20:478-480.
19. Oliveira M, Braga S, Passos-Coelho JL, Fonseca R, Oliveira J. Complete response in HER2+ leptomeningeal carcinomatosis from breast cancer with intrathecal trastuzumab. *Breast Cancer Res Treat*. 2011;127:841-844.
20. Chamberlain MC, Kormanik P, Barba D. Complications associated with intraventricular chemotherapy in patients with leptomeningeal metastases. *J Neurosurg*. 1997;87:694-699.
21. Braen APJM, Perron J, Tellier P, Catala AR, Kolaitis G, Geng W. A 4-week intrathecal toxicity and pharmacokinetic study with trastuzumab in cynomolgus monkeys. *Int J Toxicol*. 2010;29:259-267.
22. Nettis E, Calogiuri G, Colanardi MC, Ferrannini A, Tursi A. Drug-induced aseptic meningitis. *Curr Drug Targets Immune Endocr Metabol Disord*. 2003;3:143-149.
23. Kepa L, Oczko-Grzesik B, Stolarz W, Sobala-Szczygiel B. Drug-induced aseptic meningitis in suspected central nervous system infections. *J Clin Neurosci*. 2005;12:562-564.
24. Moris G, Garcia-Monco JC. The challenge of drug-induced aseptic meningitis. *Arch Intern Med*. 1999;159:1185-1193.
25. Jolles S, Sewell WAC, Leighton C. Drug-induced aseptic meningitis: diagnosis and management. *Drug Saf*. 2000;22:215-226.
26. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245.